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MINIREVIEW

Chemotherapy of Rhinovirus Colds

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INTRODUCTION

Treatment of the common cold and its complications remains a continuing challenge to physicians and other health care providers (70). Family-based studies indicate that the average preschool child experiences 6 to 10 colds per year and the average adult has 2 to 4 colds per year (46). Women, especially those aged 20 to 30 years, have more colds than men, presumably because of greater exposure to children, whereas adults ≥60 years of age average less than one cold per year. According to 1985 statistics of the National Health Interview Survey (78), colds accounted for 17% of all episodes of acute illness or injury that led to medical attention or at least 1 day of restricted activity. Common colds were associated with 161 million days of restricted activity and accounted for 26 million days of school absenteeism and 23 million days lost from work. During that year, there were about 27 million visits to physicians for colds. According to a 1980 survey, drugs were recommended during 94% of visits to physicians for upper respiratory tract infections, excluding pharyngitis, laryngitis, tracheitis, and bronchitis (20). An average of two drugs were recommended to patients per visit, and antibiotics are prescribed in about one-half (20, 23) of such visits. Most colds, however, are not medically attended. More than 800 oral nonprescription cold remedies are available (70), and the annual expenditure for various cold treatments exceeds $2 billion in the United States. Because of their frequency and associated morbidity, common colds continue to represent a significant health problem.

Goals of treatment. The principal goals in treating common colds are to reduce their sympton burden and improve the functional status of those afflicted, reduce the risk of complications, and decrease the likelihood of spreading infection to contacts. The latter could potentially be achieved by reducing concentrations of virus in respiratory secretions through a specific antiviral agent, by reducing the volume of respiratory secretions, or perhaps by modifying illness manifestations (rhinorrhea, sneezing, cough) that may be important in disseminating infection. The recognized complications of common colds include secondary bacterial infections of the paranasal sinuses (~0.5% of adults) and middle ear (~2% of adults, 5% or more of children) and exacerbations of asthma, chronic bronchitis, and emphysema (43, 46).

The pathophysiologic events following viral infection in the nasal epithelium are only partially understood. Infections caused by rhinovirus, the most common cause of colds, are associated with little evidence of cell necrosis or mucosal damage, and it appears that host responses may account for the vascular engorgement, increased vascular permeability with transudation of serum proteins, and increased mucus production that are hallmarks of common colds (Fig. 1). These responses include elaboration of inflammatory mediators, such as kinins (77); influxes of inflammatory cells, including polymorphonuclear leukocytes (77, 109); and probably neuroreflexes with associated cholinergic stimulation and neuropeptide release. Recently, intranasal instillation of bradykinin was shown to cause some of the symptoms (rhinorrhea, stuffiness, sore throat) and nasal mucus alterations observed in rhinovirus colds (D. Proud, C. J. Reynolds, S. LaCapra, A. Kagey-Sobotka, L. M. Lichtenstein, and R. M. Naclerio, Am. Rev. Respir. Dis., in press). Viral infection of the nasal mucosa is not uniform, and although the titers of virus recoverable in nasal washings are highest during the first week of infection, replication may continue for 2 to 3 weeks (116). If ongoing viral replication is essential to the development and progression of illness, then early antiviral therapy may provide symptom benefit. Alternatively, if the initial viral infection serves primarily to trigger host responses, even a rapid antiviral effect might not be helpful in symptom reduction. Agents that inhibit the action of host inflammatory mediators and treatments directed against reversible pathophysiologic consequences, such as alpha-adrenergic agonists for vascular engorgement, may offer symptom relief.

Assessment of therapeutic interventions. Various methodologic problems arise in attempting to assess therapeutic interventions for the common cold. The first is definition of the common cold, since it represents a syndrome produced by many viruses. Six different virus families including over 200 serotypes account for most colds. Rhinoviruses (30 to 50% of cases), coronaviruses (10 to 20%), and, to a lesser extent, adeno-, parainfluenza, respiratory syncytial, influenza, and enteroviruses (<5% of cases for each) are associated with this syndrome (46). Very few intervention studies of naturally occurring colds have attempted to define the viral agent or to assess outcomes based on etiology.

The familiar complaints of nasal discharge and obstruction (80 to 100% of patients), sneezing (50 to 70%), sore throat (50%), and cough (40%) are the most common symptoms, but these may occur in differing frequencies and severities and may be present in patients with vasomotor or allergic rhinitis or streptococcal pharyngitis. In addition to viral cultures, nasal smears for eosinophilia (114) or ciliocytophthoria (86, 109) may offer objective means for distinguishing between rhinitis of allergic or viral etiology. Furthermore, uncomplicated viral infections may be difficult to distinguish from those with bacterial complications. Most rhinovirus and coronavirus colds have an incubation period of 2 to 3 days, with symptoms most pronounced on day 2 or 3 of illness and duration of about 1 week. However, the incuba-

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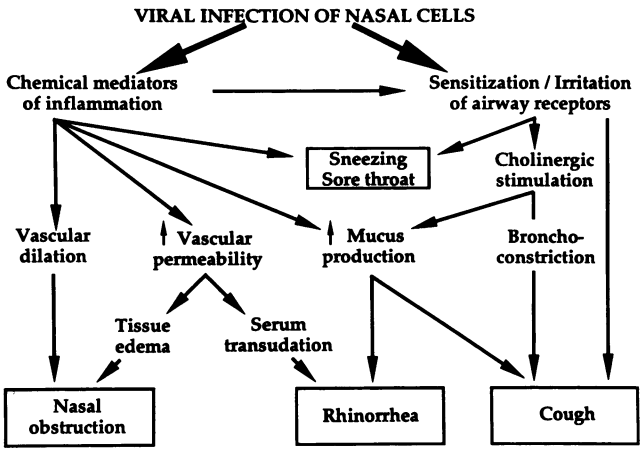

FIG. 1. Theoretical scheme of symptom pathogenesis in rhinovirus colds; adapted from Hendley (53) and from Turner et al. (109).

tion period may last up to 1 week, and up to 25% of colds may extend for 2 weeks or longer. The self-limited but variable clinical course of such illnesses means that interventions have a relatively short period to show therapeutic effects and that large sample sizes are needed to assess clinical outcomes.

Because of the paucity of useful clinical signs in common colds, subjective parameters of response, particularly patient reports of illness onset and severity, have been used for assessing treatment responses in most studies. A very significant placebo effect has been recognized in studies of natural colds. In 1933 Diehl found that 35% of patients with colds who were treated with a lactose placebo reported good results, which prompted him to state, "it is possible to convince the public that practically any preparation is of value for the prevention or treatment of colds" (22). One clinical trial of ascorbic acid showed that the apparent benefit in the vitamin C recipients was accounted for by volunteers who had tasted the contents of their capsules and correctly identified their treatment. Reanalysis with omission of these subjects found no evidence of a treatment benefit (14, 61). Other studies of experimentally induced rhinovirus colds (99) and field trials of natural colds, including studies of identical twins (13, 71, 75), have found that ascorbic acid provides no clinically important prophylactic or therapeutic effects on respiratory illness frequency or severity (40, 93). Such observations underscore the necessity for adequate controls and appropriate blinding of studies. Subjective assessments in such trials are not valid if the subjects determine that they are receiving the active treatment, owing to the perception of other drug effects. As discussed below, such problems were recently encountered in some efficacy studies of zinc gluconate lozenges for treatment of colds.

Objective measures of response to treatment, such as viral shedding, nasal mucus weights, counts of paper tissues, cough counts, rhinomanometric measures of nasal patency (18, 27), and, recently, measures of eustachian tube function and middle ear pressure, have been used in studies of experimentally induced colds but in few studies of naturally occurring colds. Experimental challenge models have been established which accurately reproduce cold symptoms and signs and allow for evaluation of objective parameters. Studies of experimentally induced rhinovirus colds also offer the advantages of using relatively homogeneous groups of susceptible adults (based on serum neutralizing antibody to the challenge virus) in whom high infection (≥90%) and illness (50 to 80%) rates are reproducibly observed and in whom the virologic course of infection can be readily monitored. Similar to natural colds, about one-third of experimentally induced infections are subclinical, and the severity of illness is variable in the remainder. Thus, because of the relatively small sample sizes possible in such challenge studies, they have a low statistical power to detect small therapeutic effects.

ANTIVIRAL CHEMOTHERAPY

A wide range of compounds have been found to have antirhinoviral activity under in vitro conditions (Table 1). Many of these have been abandoned for clinical purposes because of problems with toxicity, unfavorable pharmacology, or insufficient potency. It is noteworthy that some of the traditional folk remedies may have or be capable of stimulating antiviral activity. For example, it has been suggested that radix astragali seu hedysari, used in traditional Chinese medicine, may stimulate immunoglobulin A production and induce interferon production when given orally or by aerosol (117, 118). Additionally, a flavone isolated from the Chinese medicinal herb agastache folium has potent antipicornaviral activity (57). Certain plant drugs used in Unani (Greco-Arab) medicine for the treatment of common colds also possess in vitro antiviral activity (110). This review focuses on those agents that have undergone recent testing in controlled trials of experimentally induced or naturally occurring common colds (Table 2).

Interferon. Natural and recombinant human interferons have received the most comprehensive clinical testing of available antiviral agents. Intranasal administration of recombinant interferon alfa-2 (rIFN-α_2) is effective for prevention of experimentally induced rhinoviral and coronaviral infections (reviewed in reference 47). Prophylactic efficacy against natural rhinovirus colds has been observed at rIFN-α_{2b} dosages of 3 to 10 MU/day when administered during peak periods of rhinoviral activity in the community (47, 76) and at dosages of 5 MU/day administered for 1 week after exposure to illness in the family setting (26, 48). However, long-term intranasal administration of natural or recombinant IFN-α is associated with nasal irritation that appears to be preceded by interferon-induced mucosal histologic changes, particularly lymphocytic infiltration (52). The interferon prophylaxis studies have clearly shown that it is possible to effectively use intranasal delivery of antiviral agents.

In contrast to its prophylactic use, intranasal interferon administered therapeutically has been associated with discouraging results. One study of experimentally induced rhinovirus colds, in which rINF-α_2 at 27 MU/day was begun at 28 h after viral challenge, found that administration by nasal drops but not by nasal spray was associated with significant reductions in the quantity and duration of viral shedding and with modest reductions in nasal symptoms and mucus production (50). Another study with leukocyte-derived human IFN-α at 23 MU/day found no significant reductions in the clinical or virologic course of infection when treatment was begun 40 h after viral inoculation (90). One study of natural colds, in which patients used rINF-α_{2a} sprays (12 MU/day) within 24 h after the onset of symptoms, found no significant symptom benefit compared with placebo (M. Just, R. Berger, O. Ruuskanen, M. Ludin, and S. Linder, J. Interferon Res. **6**:32, 1986). In another study, 220

TABLE 1. Representative antiviral agents with activity against rhinovirus

Agent	Reference(s)
Interferons	
rIFN-α_{2b}	47, 48, 50, 51[a]
rIFN-α_{2a}	47; Just et al., J. Interferon Res. 6:32, 1986[a]
rIFN-β_{serine}	Hayden et al., J. Interferon Res. 6:31, 1986[a]
Interferon inducers	
Poly I:C	55[a]
N,*N*-Dioctadecyl-*N*′,*N*′-bis-(2-hydroxyethyl)-propanediamine (CP-20,961)	24, 38, 85[a]
Capsid-binding agents/inhibitors of uncoating	
4′,6-Dichloroflavan (BW 683C)	6, 91[a]
4′-Ethoxy-2′-hydroxy-4,6′-dimethoxychalcone (Ro 09-0410)	5b, 57, 58, 82[a]
5-Ethoxy-3-methoxy-2-(*p*-methoxy-*trans*-cinnamoyl)phenylphosphate (Ro 09-0415)	57, 89[a]
1-(5-Tetradecyloxy-2-furanyl)ethanone (RMI 15,731)	9; Gwaltney and Hayden, 23rd ICAAC[a]
2-[-(1,5,10,10a-Tetrahydro-3*H*-thiazolo[3,4b]isoquinolin-3-ylindene)amino]-4-thiazole acetic acid (44,081 R.P.)	119[a]
Disoxaril, 5-[7-[4-(4,5 dihydro-2-oxazolyl)phenoxy]heptyl]-3-methyl-isoxazole (WIN 51,711)	73, 84
5-[5-[2,6-Dichloro-4-(4,5-dihydro-2-oxazolyl)phenoxy]pentyl]-3-methylisoxazole (WIN 54954)	M. J. Otto, G. D. Diana, M. A. McKinlay, P. Felock, and M. Farcher, 27th ICAAC, abstr. no. 491, 1987
3-Methoxy-6-[4-(3-methylphenyl)-piperazinyl]pyridazine (R61837)	5c; Al-Nakib et al., 7th Int. Congr. Virol.; K. Andries, B. Dewindt, M. De Brabander, and R. Stokbroeckx, Abstr. 7th Int. Congr. Virol., abstr. no. 32.7, 1987[a]
3,4-Dihydro-2 phenyl-2*H*-pyrano[2,3-b]pyridines	10, 62
Phenoxypyridinecarbonitriles	63
2-(3,4-Dichlorophenoxy)-5-nitrobenzonitrile (MDL 860)	94, 108
Benzimidazoles	44, 83, 101
Enviroxime, 2-amino-1-(isopropyl sulfonyl)-6-benzimidazole phenyl ketone oxime	21, 49, 69, 74, 88, 92[a]
1′-Methyl spiro(adamantane-2,3-pyrrolidine)maleate	72[a]
Isatin thiosemicarbazone	42
Fusidic acid	2[a,b]
Substituted triazinoindoles	45, 60
4-([8-Amino-7-chloro-5-methyl-5*H*-*as*-triazino(5,6-b)indol-3-yl]amino)-2-methyl-2-butanol (SK&F 40491)	97[a]
2,6-Diphenyl-3-methyl-2,3-dihydroimidazo[2,1-b]thiazole (RP 19326)	97[a]
3-Alpha-naphthyl-5-diethylcarbamoyl-1,2,4-oxadiazole (GL R9-338)	97[a]
Oxolinic acid	60[a]
Isoquinolines	
1-(*p*-Chlorophenoxymethyl)-3,4-dihydroisoquinoline hydrochloride (UK-2054)	96[a]
3,4-Dihydro-1-isoquinolineacetamide hydrochloride	107[a]
1-*p*-Chlorophenyl-3-(*m*-3-isobutyl-guanidinophenyl)urea hydrochloride (ICI 73,602)	97
Zinc salts	5a, 25, 28, 32, 39, 66; Smith et al., Clin. Res. 35:761A, 1987[a]

[a] Including clinical trials conducted with humans.
[b] Studies evaluated activity against coxsackie A21 virus.

TABLE 2. Summary of efficacy data on antiviral agents tested in placebo-controlled trials for early treatment of rhinovirus colds

Treatment (reference)	Route[a]	Dosage[b]	Duration (days)	Total no. of subjects	Reduction (% change) compared with placebo[c]		
					Symptoms	Days of viral shedding	Nasal mucus wt
Experimental colds							
IFN-α_2 drops (50)	i.n.	9 MU t.i.d.	5	29	± (25)	+ (54)	± (53)
IFN-α_2 spray (50)	i.n.	9 MU t.i.d.	5	23	0	+ (35)	0
IFN-α (90)	i.n.	23 MU/day	4	25	0	0	0
Enviroxime (92)	i.n.	568 μg 6 times per day	5	55	0	0	0
Enviroxime (69)	i.n.	568 μg q.i.d.	4–6	60	0	0	NR
Zinc gluconate (32)	p.o.	23 mg 8 times per day	5	32	0	0	0
	p.o.	23 mg 8 times per day	7	45	0	0	0
Zinc gluconate (5a)	p.o.	23 mg every 2 h while awake	6	12	+ (34)	0	+ (57)
Natural colds							
IFN-α_{2b} (51)	i.n.	2.5 or 5 MU q.i.d.	5	220	0	+	NR
IFN-α_{2a} (54)	i.n.	0.15 or 0.75 MU b.i.d.	5	189	0	NR	NR
Enviroxime (74)	i.n.	2,720 μg 6 times per day for 2 days 2,720 μg q.i.d. for 5 days	7	290	0	0	NR
Zinc acetate (25)	p.o.	10 mg 6–8 times per day	3–6	55	0	NR	NR
Zinc gluconate (28)	p.o.	23 mg every 2 h	—[d]	80	+	NR	NR
Zinc gluconate (Smith et al., Clin. Res. 35:761A, 1987)	p.o.	23 mg every 2 h	—[e]	110	0	NR	NR

[a] i.n., intranasal; p.o., oral.
[b] t.i.d., Three times per day; q.i.d., four times per day; b.i.d., twice a day.
[c] +, Significant; ±, trend; 0, not significant; NR, not reported.
[d] Until resolution of symptoms.
[e] Up to 7 days or 24 h after resolution of symptoms.

subjects with cold symptoms of ≤48-h duration, 59% of whom were proven to be rhinovirus infected, were randomized to receive intranasal sprays of rIFN-α_{2b} at 10 or 20 MU/day or placebo for 5 days (51). The median duration of colds tended to be longer by 2 days in the high-dose interferon group than in the other groups, and no differences favoring interferon treatment were found in respiratory symptom scores or the times to resolution of specific symptoms. Even in those with proven rhinovirus colds treated within 24 h of symptom onset, the high-dose interferon recipients tended to have more prolonged symptoms than did placebo recipients. Interferon-treated patients also had significantly higher frequencies of blood-tinged nasal mucus. An antiviral effect of intranasal interferon was demonstrated by a reduced frequency of rhinovirus recovery on study days 5 (15 versus 48%) and 7 (13 versus 50%) compared with placebo, but no difference between the treatment groups in new respiratory illness occurrence was observed in the household contacts. These observations indicated that nasal sprays of rIFN-α_{2b} were not effective for treatment of natural colds, had incomplete antiviral effects, and were associated with discernible side effects (51). It remains to be determined whether other interferons (F. G. Hayden, D. J. Innes, S. E. Mills, and P. A. Levine, J. Interferon Res. 6:31, 1986), combinations of interferons (4), or alternate methods of administration can improve antiviral activity and reduce local toxicity.

Enviroxime. Enviroxime, a benzimidazole derivative with potent in vitro antirhinoviral activity, is one of the more extensively studied synthetic agents. Noncytotoxic concentrations of enviroxime are associated with complete inhibition of replication of 83 rhinovirus serotypes (21). The 50% inhibitory concentration ranges from <0.01 to 0.12 μg/ml for different serotypes. The mechanism of action of enviroxime is not completely understood, but it is believed that the drug inhibits the formation of the viral RNA polymerase replication complex (E. Wu, personal communication).

Studies of oral enviroxime reported low levels in blood and nasal secretions and a high frequency of nausea and vomiting (49). When enviroxime is applied topically to the nasal mucosa, concentrations exceed 0.2 μg/ml by at least 50-fold for up to 6 h after administration. When used for prophylaxis of experimental rhinovirus colds, combined administration of low-dose oral drug (25 mg) and nasal spray (568 μg) four times daily tended to reduce symptoms and quantitative virus titers and significantly reduced nasal mucus production compared with placebo (88). In contrast, studies of intranasal enviroxime alone (568 μg five times daily) did not find significant reductions in illness or infection rates, mucus production, or frequency of viral shedding compared with placebo (49).

No therapeutic benefit was found in one study with four sprays per day (69), and only modest symptom benefit without reductions in viral shedding or mucus weights was found in another study with six sprays per day starting 44 h after rhinoviral challenge (92). A family-based field treatment study demonstrated no significant advantage of intranasal enviroxime spray (2,720 μg six times daily for the first 2 days followed by four times daily for an additional 5 days) in naturally occurring rhinovirus colds compared with placebo (74). Thus, despite its potent in vitro antirhinoviral activity, significant therapeutic benefit has not been seen with oral or intranasal administration. Chemically related derivatives, such as enviradene (105), which retain antirhinoviral activity in vitro and have improved oral bioavailability, and the use of alternative topical delivery methods, such as incorporation into liposomes (B. E. Gilbert, H. R. Six, S. Z. Wilson, P. R. Wyde, and V. Knight, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 986, 1987), remain under investigation.

Zinc salts. Studies conducted in the mid-1970s found that relatively high concentrations (~0.1 mM) of zinc chloride inhibit the in vitro replication of representative rhinovirus serotypes (66). This effect appears to be mediated through

inhibition of viral polypeptide cleavage (65). More recent studies have found that zinc salts have relatively weak, nonselective antirhinoviral activity in WI-38 strain human embryonic lung and HeLa cell cultures (39).

One clinical trial reported that zinc gluconate lozenges (23 mg) dissolved in the mouth every 2 h while the subjects were awake were associated with dramatic reductions in the duration of common cold symptoms (28). However, this study was confounded by high dropout and side-effect (unpalatable taste and mouth irritation) rates in the zinc group, an inexplicably long duration of illness in the placebo group, and the use of a nonmatched placebo lozenge that resulted in ineffective blinding of the study. Since patients experiencing side effects of zinc would be more likely to believe that they were on active medication and because the study design allowed subjects to stop treatment once their symptoms had resolved, a significant reporting bias was probably introduced into the study. Patients may have reported resolution of cold symptoms in order to discontinue taking the distasteful lozenges, or perhaps the modest symptoms related to the cold could have been masked by the unpleasantness of the lozenges (33).

A subsequent placebo-controlled study of experimentally induced colds found that zinc gluconate lozenges taken every 2 h while the subjects were awake before and for several days after experimental rhinoviral inoculation did not significantly reduce viral shedding, overall symptoms, or nasal mucus production (5a). The same investigators reported that therapeutic administration beginning on the first day of illness after experimental rhinoviral challenge was associated with significant reductions in symptoms but no effect on quantitative viral shedding (5a). However, this study was flawed by very small sample sizes in the zinc and placebo groups. Two other trials of experimental rhinovirus colds, in which treatment with zinc gluconate or a taste-matched placebo was begun at 2 or 36 h after inoculation, found no antiviral effects or reductions in the severity or duration of cold symptoms or in nasal mucus production, despite significant increases in serum zinc levels (32). To achieve satisfactory placebo matching for the zinc lozenges, the bitter substance denatonium benzoate, which is used to discourage thumb sucking in children, was used in the placebo. Similarly, field trials of naturally occurring common colds have failed to document clinically important effects from zinc acetate lozenges (25) or zinc gluconate lozenges (D. S. Smith, C. E. Nuttall, E. C. Helzner, B. A. Rofman, C. B. Goswick, A. Magner, and M. Collins, Clin. Res. 35:761A, 1987) compared with taste-matched placebos. These trials, as well as formal taste tests, have found high rates of unpleasant aftertaste (75% of subjects), nausea (30%), and mouth soreness (50%) to be associated with zinc lozenge administration (33). A study of healthy adult males also found that long-term zinc ingestion (300 mg/day for 6 weeks) is associated with significant reductions in lymphocyte proliferative responses, polymorphonuclear phagocytic function, and high-density lipoprotein concentrations (15). The current evidence indicates that oral administration of zinc salts is not associated with in vivo antirhinoviral activity or with clinically important activity in common colds. Given their high frequency of unpleasant side effects, zinc salt lozenges cannot be recommended for prevention or treatment of common colds.

Capsid-binding agents. A number of compounds have in vitro activity against rhinovirus mediated through binding directly to the virus capsid (Table 1). Other antiviral mechanisms of action have been described for some of these agents (reviewed in reference 100). Most are rhinovirus specific, but all of these agents have substantial serotype-related variability in antiviral activity. The concentrations inhibiting rhinoviral replication in vitro may vary up to 1,000-fold for different serotypes (57, 84). Several of these agents (such as Ro 09-0410) cause contact inactivation of rhinoviral infectivity (58), whereas others cause inhibition of replication only if the compound is present at the time of cellular infection. These are believed to inhibit rhinovirus uncoating through stabilization of the protein capsid of the virus and prevention of the conformational changes required for release of viral RNA (5, 35, 82, 106). X-ray crystallographic structural analysis has determined that the precise binding site of disoxaril (WIN 51,711) to rhinovirus type 14 is the interior of viral protein 1 (VP1) (103). Changes in the amino acids of this binding pocket may affect the ability of a specific agent to bind to the capsid and thus explain the different susceptibilities of different rhinovirus serotypes. The binding sites for some of these agents may be the same or lie very close to one another. For example, strains of rhinovirus resistant to dichloroflavan and RMI 15,731 display cross-resistance to Ro 09-0410 and vice versa, but not to enviroxime, which is not a capsid binder. Similarly, binding of radiolabeled Ro 09-0410 to rhinovirus type 2 is inhibited by unlabeled Ro 09-0410, dichloroflavan, and RMI 15,731, but not by enviroxime (81). Another potential limitation with the use of these compounds is that drug-resistant mutants can be selected readily under in vitro conditions (100). One study of disoxaril found low-level resistance (2-fold increase) at 10^{-3} to 10^{-4} and high-level resistance (40-fold increase) at 10^{-5} mutants per plaque (B. Heinz and R. Rueckert, Abstr. 7th Int. Congr. Virol., abstr. no. 32.13, 1987). Another study found that chalcone-resistant rhinovirus type 9 had altered growth characteristics compared with the parent strain, a finding which could mean reduced virulence (3).

Clinical trials have found discrepancies between the in vivo and in vitro antiviral activities of these compounds. Orally administered dichloroflavan, 1 mg/kg (body weight) three times daily, was ineffective in the prophylaxis of experimental rhinovirus colds (91). Despite adequate levels in plasma, drug was not detected in nasal washings, and no antiviral effect was found (91). A subsequent study determined that intranasal administration of dichloroflavan was tolerated and resulted in high nasal wash concentrations for 3 to 3.5 h after administration (6). However, nasal drops of dichloroflavan, 40 mg five times daily, failed to reduce infection rates or protect against illness after experimental rhinoviral infection. These findings suggest that despite high levels in nasal washings, adequate levels were not achieved in nasal mucosal cells (6).

The synthetic chalcone Ro 09-0410, which has potent in vitro antirhinoviral activity, is related to an antiviral flavone originally isolated from a Chinese medicinal herb (57, 59, 82). Because of poor absorption when it is administered orally, a phosphorylated ester, Ro 09-0415, was developed in an attempt to achieve adequate levels in blood after oral administration. Ro 09-0415 is well absorbed and relatively nontoxic to humans but was ineffective at dosages of 1,200 mg twice daily in preventing illness in experimental rhinoviral infections (89). Despite adequate levels of Ro 09-0410 and Ro 09-0415 in blood, drug was undetectable in nasal wash specimens. An intranasal preparation of Ro 09-0410 provided no protection against experimental rhinoviral infections and was associated with increased nasal mucus production compared with placebo (5b).

The antiviral agent RMI 15,731 administered as 200 μg

intranasally five times daily did not protect against illness after experimental rhinoviral challenge (J. M. Gwaltney, Jr., and F. G. Hayden, 23rd ICAAC, abstr. no. 931, 1983). This is similar to the findings with intranasal enviroxime and raises the question of whether such hydrophobic drugs are able to penetrate through the nasal mucus to reach the mucosa. The compound 44,081 R.P. differs from other capsid-binding agents in that it is soluble in aqueous solutions and appears to interact with uninfected host cells to impart residual antiviral activity (119). However, a trial of 44,081 R.P. administered as an intranasal spray (600 μg six times daily) revealed no prophylactic effect against experimental rhinoviral infection (119). Drug levels in nasal washings 2 h after administration averaged only 2.5-fold higher than the inhibitory concentration for the challenge virus.

Recently, a new antirhinovirus compound (R61837) which inhibits the in vitro replication of 74% of serotypes at concentrations below 10 μg/ml has been described (5c). When administered intranasally in frequent doses beginning 1 h before and continuing for 6 days after experimental rhinoviral challenge with a very susceptible serotype (inhibitory concentration, <0.01 μg/ml), it was associated with marked reductions in nasal symptoms and mucus weights (W. Al-Nakib, P. G. Higgins, D. A. J. Tyrrell, I. G. Barrow, N. Taylor, and K. Andreis, Abstr. 7th Int. Congr. Virol., abstr. no. 32.3, 1987). Therapeutic studies are in progress.

Rhinovirus receptor blockade. Picornaviruses initiate infection and enter into host cells by attaching to host cell receptors. Nearly 90% of human rhinovirus serotypes (the major group) share a single type of cellular receptor (1, 17). The remaining serotypes (the minor group) have a different cellular receptor. Murine monoclonal antibodies directed against the major group receptor site compete with rhinovirus and coxsackie A viruses for binding in vitro and are able to displace previously bound virions from the receptor (17). Prophylactic intranasal administration of one of these murine monoclonal antibodies to humans was recently shown to modify the clinical and virologic course of experimental rhinoviral infections (F. Hayden, J. Gwaltney, Jr., and R. Colonno, Antiviral Res., in press). The development of synthetic receptor blocking agents may offer a novel approach to the prophylaxis and possibly early treatment of rhinoviral or other viral infections.

SYMPTOMATIC THERAPY

The various symptomatic therapies for common colds were recently considered elsewhere (70), and this review addresses only some of these drugs.

Antihistamines. Antihistamines of various classes that block the H_1 receptor are commonly used alone or in combination with other drugs for symptomatic relief of common colds. In contrast to allergic rhinitis, for which histamine release is important in the pathogenesis of symptoms and for which antihistamine therapy is of proven value, histamine concentrations do not change in nasal secretions during the course of rhinovirus colds (29, 77). In other viral infections, particularly respiratory syncytial and parainfluenza viral infections in children, histamine release may be important in the pathogenesis of lower respiratory tract illness (102, 111, 112).

In their 1975 review of studies of antihistamines for common colds, West and co-workers concluded that only 2 of 35 reported studies had both precise enrollment-outcome criteria and an appropriate trial design and that the results of these two studies did not support the use of antihistamines to prevent or treat cold symptoms (113). Recent controlled trials with alkylamine-type antihistamines (e.g., chlorpheniramine and triprolidine) have reported reductions in certain symptoms of natural colds (12, 19, 56). One multicenter study (56) of oral chlorpheniramine reported statistically significant but modest (generally <10 to 15%) reductions in symptoms of nasal discharge, sneezing, and nose blowing, compared with placebo. No symptom benefit was seen in one of the three study centers, and an excess frequency of drowsiness was reported in the chlorpheniramine group. It is possible that the sedating effect of antihistamines may alter the perception of symptoms and/or lead to a biased reporting of symptoms by treated patients. Another study of natural colds (12), in which patients were randomly assigned to receive oral pseudoephedrine, triprolidine, pseudoephedrine and triprolidine, or placebo, found a significant reduction in sneezing on treatment day 2 in the triprolidine group compared with the placebo group but no overall significant symptom benefit. The group given combined therapy did no better than those treated with pseudoephedrine alone. The dosages of chlorpheniramine and triprolidine used in these studies have been associated with both excess rates of sedation and impaired performance on psychomotor tests in healthy adults, compared with placebo (16, 67, 79, 80). Placebo-controlled studies of experimentally induced rhinoviral infection found no evidence of reduction in nasal symptoms or mucus production with oral or intranasally administered antihistamines (34, 37) (Table 3). Terfenadine, an H_1 selective antihistamine with lower potential for causing sedation and lacking anticholinergic activity, has been found to be no different from placebo in treating natural colds (M. J. Gaffey, D. L. Kaiser, and F. G. Hayden, Pediatr. Infect. Dis., in press).

In regard to preventing the development of complications, one controlled trial found that treatment of common colds with both an oral decongestant (phenylpropanolamine) and antihistamine (brompheniramine maleate) did not reduce the risk of secondary otitis media in preschool-age children (5.8% attack rate) compared with placebo (6.4%) (95). A 9-month study of 44 children with recurrent otitis media found that prophylactic administration of this drug combination did not reduce the occurrence of respiratory tract symptoms or otitis episodes compared with placebo (64). In summary, controlled clinical trials of natural colds have found little evidence that antihistamines provide clinically important benefits. It is likely that any antisecretory effect of antihistamines relates to their anticholinergic (atropinelike) activity.

Sympathomimetics. The most commonly used symptomatic treatments for colds include topical and systemically administered decongestants. These alpha-adrenergic agonists constrict the microvasculature of the nasal mucosa and are postulated to relieve nasal congestion by reducing blood flow in the highly vascular mucosa and by shrinking venous capacitance vessels over the middle and inferior turbinates and septum. The widely used oral agents (phenylpropanolamine, pseudoephedrine) are alpha- and beta-adrenergic agonists that have an indirect sympathomimetic effect through the release of norepinephrine from neuronal storage sites and direct effects on alpha-adrenergic receptors (reviewed in references 30 and 87). Controlled trials with standard dosages of phenylpropanolamine and pseudoephedrine have found significant reductions (approximately 35 to 55%) in nasal airflow resistance determined by rhinomanometry in patients with natural colds (27, 68, 98). These

TABLE 3. Effect of various symptomatic therapies on nasal secretion in volunteers with experimental rhinovirus colds (University of Virginia)

Treatment group (reference)	Route of administration[a]	Dosage[b]	No. of subjects	Mucus wt (g/5 days)	Reduction in nasal secretions (% decrease compared with placebo)[c]
Pseudoephedrine (Sperber et al., 27th ICAAC)	p.o.	60 mg q.i.d.	22	16	+ (41)
Placebo			9	27	
Atropine methonitrate (36)	i.n.	250 μg q.i.d.	9	20	± (47)
Placebo			7	38	
Ipratropium (unpublished observations)	i.n.	80 μg t.i.d.	34	15	± (40)
Placebo			35	25	
Diphenhydramine (37)	i.n.	2.0 mg q.i.d.	12	24	0
Placebo			11	24	
Chlorpheniramine (37)	p.o.	4.0 mg q.i.d.	13	8[d]	0
Placebo			15	8[d]	

[a] p.o., oral; i.n., intranasal.
[b] q.i.d., Four times per day; t.i.d., three times per day.
[c] +, Significant difference; ±, trend; 0, no difference.
[d] Collections obtained only on days 3 to 6 after challenge.

increases peak at 1 h and last for at least 4 h after single oral doses. The degree of symptom benefit provided by repeated doses of oral decongestants is less clear. One study of natural colds found that pseudoephedrine reduced symptoms of sneezing and congestion on several treatment days and significantly increased the overall perception of improvement (53% of subjects) compared with placebo (25%) (12). A recent double-blind, placebo-controlled study of experimental rhinovirus colds found a 48% reduction in total symptoms and a 41% decrease in nasal mucus weights with pseudoephedrine treatment (60 mg four times daily) (S. J. Sperber, J. M. Gwaltney, Jr., J. V. Sorrentino, and F. G. Hayden, 27th ICAAC, abstr. no. 501, 1987) (Table 3). Although oral decongestants could possibly cause decongestion of the mucosa in the sinuses or eustachian tube, almost all studies have found no evidence of therapeutic benefit in established acute otitis, serous otitis, or acute sinusitis (reviewed in reference 8).

Doses large enough to reverse nasal vascular congestion would be expected to cause vasoconstriction in other vascular beds and raise blood pressure. This risk appears to be greater with phenylpropanolamine than pseudoephedrine (87). These agents have been associated with serious toxicities (87), but the infrequency of reports despite widespread use suggests that this is a relatively low risk in otherwise healthy individuals.

Topical application of nasal sympathomimetics like phenylephrine and oxymetazoline provides rapid vasoconstrictive effects in the mucosa and associated increases in nasal patency and subjective decongestion. Other symptoms, including rhinorrhea and cough, are not relieved, and some laboratory evidence suggests that alpha-agonists may actually provoke increased mucus production. However, controlled trials with topical oxymetazoline (115) and orally administered pseudoephedrine have not found evidence of increased nasal mucus production compared with placebo (Table 3). The imidazoline derivatives like oxymetazoline have both alpha 1 and alpha 2 agonist activity and longer duration of action but may also be associated with a greater risk of nasal irritation. One study found that topical application of an alpha 2-adrenergic agonist reduced nasal mucosal blood flow in the human nose in contrast to the alpha 1 agonist phenylephrine (7). In addition to systemic adverse effects (31), the use of these preparations is frequently associated with rebound congestion, perhaps related to vasoconstrictive ischemia and membrane irritation, after 3 or 4 days of use.

Anticholinergics. Activation of the parasympathetic nervous system has been postulated to be important in the production of rhinorrhea and perhaps other nasal symptoms during the common cold (Fig. 1). Cyclic anticholinergic compounds can be topically delivered to the respiratory tract with minimal risk of systemic side effects. Intranasal administration of the quaternary cholinergic agonist ipratropium bromide inhibits the normal nasal secretory response to methacholine. One double-blind trial (11) of common colds in adults found that ipratropium nasal spray (80 μg four times daily for 7 days) in conjuction with intranasal xylometazoline was associated with significant reductions (33 to 48%) in paper tissue use during the first 3 days of illness compared with the vasoconstrictor spray alone. No reduction in sneezing was observed. Unfortunately, this study involved a relatively small number of subjects with colds of undefined etiology and did not directly measure mucus production. In volunteers with experimentally induced rhinovirus type 39 infection, intranasal ipratropium (80 μg twice daily for 5 days) starting 24 h after viral challenge was associated with approximately 40% reduction in mucus weights compared with placebo (Table 3). In similar studies with another quaternary cholinergic antagonist, atropine methonitrate, higher intranasal dosages (250 μg four times daily for 5 days), but not lower (125 μg twice daily) dosages, were also associated with reductions in nasal mucus production but not in nasal symptoms (36). These findings suggest that cholinergic mechanisms play a role in the pathogenesis of nasal mucus production during rhinovirus colds, but the overall clinical value of topical anticholinergics remains to be determined. It is possible that excessive drying of secretions could worsen symptoms or increase the possibility of complications. The use of systemic belladonna alkaloids, such as atropine, in oral cold remedies has not been critically evaluated.

Nonsteroidal antiinflammatory drugs. Aspirin and acetaminophen are also commonly administered during colds. Both have analgesic and antipyretic properties, although fever is not a major manifestation of the common cold. One study of aspirin at 600 mg three times daily beginning during the incubation period of experimental rhinoviral infections found not only modest clinical benefit but also a significantly increased frequency of viral shedding in aspirin recipients compared with placebo recipients (104). Such an effect could result in an increased risk of transmitting infection to contacts. However, another study (W. J. Mogabgab and B. Pollock, Letter, J. Am. Med. Assoc. **235**:801, 1976) found no increase in viral shedding in experimental rhinoviral infection when aspirin was started at the onset of symptoms. A recent study of experimental rhinoviral infections, in which pseudoephedrine-treated volunteers were also given ibuprofen at 200 mg four times daily or placebo, found no increase in the frequency, duration, or quantity of viral shedding in ibuprofen recipients (Sperber et al., 27th ICAAC). Aspirin at a dosage of 16 mg/kg has also been shown to reduce lung mucociliary clearance and the tracheal mucociliary transport rate in healthy volunteers (41). The potential relevance of this finding to the common cold is not known. Aspirin and other nonsteroidal antiinflammatory agents may provide relief of some cold-related symptoms, such as sore throat or headache, but their clinical value is not clearly established in carefully controlled studies.

IMPLICATIONS

Effective treatment for the common cold remains an elusive goal. The use of specific antiviral therapy for the principal viral pathogen, rhinovirus, has been hindered by a lack of potent inhibitors, drug toxicity, and inadequate drug delivery to sites of viral replication in the nasal mucosa. Evidence suggests that if a drug does not enter nasal secretions in concentrations which are inhibitory in vitro it will not be active following oral administration. For topically applied agents, drug delivery systems or vehicles that enhance penetration of mucociliary clearance mechanisms and the use of agents that have residual biologic activity may increase their antiviral effect. Nasal wash drug concentrations do not provide a clear assessment of drug activity following topical application, and a better understanding of intranasal drug pharmacology is needed.

The relationship between ongoing viral replication and pathogenesis of symptoms in common colds is uncertain, and it remains to be determined whether prompt inhibition of viral replication would ameliorate illness in established infections. Symptomatic therapies, particularly oral or intranasal sympathomimetics, may provide short-term clinical relief, but all of the available symptomatic treatments for common colds have associated side effects. An improved understanding of the role of host inflammatory mediators in causing symptoms may enable the development of drug therapies, such as antagonists of kinin or leukotriene effects, that might provide greater symptomatic benefit. No intervention has been shown to reduce the risk of complications or of spreading infection to close contacts, although the number of studies assessing these possibilities is small.

A number of efficacy trials of treatment for the common cold have been flawed by inadequate placebo blinding, inappropriate study design, or small sample sizes. The evaluation of any treatment or prophylaxis regimen requires rigorously controlled clinical trials. The efficacy of blinding is a key element in determining the validity of such trials. Optimally, data showing proof of acceptable placebo blinding should be included in future efficacy studies of treatment for the common cold.

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